REMARKS

Claims 1-17 are all the claims pending in the application.

Claims 1-9, 11 and 13-17 are rejected under 35 U.S.C. § 112, first paragraph because of the specification.

Claims 1-9, 11 and 13-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-17 are rejected under 35 U.S.C. 102)(b) as being anticipated by Iliadis et al. (Computers and Biomedical research (2000) Vol. 33, pages 211-226; PTO-1449 Reference 30).

The Applicants traverse the rejections and request reconsideration.

Detailed Description

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Rejection of Claims 1-9, 11 and 13-17 under 35 U.S.C. § 112, second paragraph

In the discussions below, portions of the Office Action are reproduced below followed by the Applicants' response thereto

Claim 1, step (a) recites "performing a preclinical phase in which a computer model for pk/pd of the drug is created and adjusted based upon in vitro and in vivo studies in animals". It is unclear as to what the model is based upon about these particular studies? Is it based upon drug interactions that up regulate or down regulate cells in vivo, for example. What exactly constitutes the model? Clarification is requested.

The Applicants respectfully submit that PK/PD modeling is a standard procedure in pharmacology (for example, see the book Pharmacokinetics by Milo Gibaldi and Donald Perrier http://www.amazon.com/gp/reader/0824762649/ref=sib_dp_top_toc/104-6022814-4121541?ie=UTF8&p=S00B#reader-link)

Such PK/PD modeling is part of phase I clinical trials. Phase I is described in wikipedia clinical trial page (http://en.wikipedia.org/wiki/Clinical_trial) as follows:

"Phase I trials are the first-stage of testing in human subjects. Normally a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (Pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a therapy."

Pharmacokinetics and pharmacodynamics are defined in Wikipedia as follows:

Pharmacokinetics is a branch of pharmacology dedicated to the study of the time course of substances and their relationship with an organism or system. In practice, this discipline is applied mainly to drug substances, though in principle it concerns itself with all manner of compounds residing within an organism or system, such as nutrients, metabolites, endogenous hormones, toxins, etc.

Pharmacodynamics is the study of the biochemical and physiological effects of drugs and the mechanisms of drug action and the relationship between drug concentration and effect. It is often summarily stated that pharmacodynamics is the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug.

A Pharmacokinetics (PK) model constitutes equations that compute the concentration of the drug in the relevant tissue/s over time, while the Pharmacodynamics (PD) model constitutes equations that compute the effect of given concentration of the drug on the organism along time.

These model computations also referred as simulations, are essentially predictions. After conducting in vitro and in vivo studies in animals, regarding the concentration of a given drug and its effects along time, one can compare the results of the real life studies to the predictions of the models. In case these prediction turn out to be not as accurate as required, the model should be changed/ adjusted so that it gives more accurate results. The models are adjusted by changing the equations to result different outcomes to the same calculations.

Claim 1, step (b) recites "performing a phase I clinical research in which a clinical trial on at least a single dose is performed in parallel with performing computer simulation studies using the computer model". It is unclear what is being simulated by using the model? Is the model simulating the clinical research? Clarification is requested.

The model is the model of the disease in question along with the given drug model. This model describes the evolution of the disease along time and the way it is affected along time by the administration of a certain amount of a given drug. Again, the model constitutes equations for computing the effects of the drug on the disease, where the actual computation is done by computer programs. The execution of these computer programs is referred to as computer simulations, as it **simulates** on the computer **the real life disease process and the way the disease and organism is affected by a given treatment**.

For example, assume we have a model for cancer and the drug in question is Doxorubicin. We may use the model to simulate how a tumor of size *x* is affected (grow or shrink) along one year after applying 75mg of Doxorubicin once every three weeks for 6 times.

Claim 1, step (c) recites "adjusting the computer model based upon comparison of the results of the clinical research and the computer simulation". What about the computer simulation is being compared to the clinical research? Are the similarities, differences, or both being compared, for example? Clarification is requested.

The outcomes of the computer simulation, that is, the prediction of the effects of a certain drug protocol on a disease process (i.e. tumor size in certain time points), is compared to results of a real life clinical trial in which a real patient with the same disease is administered the same drug using the same treatment protocol. All real life effects of the drug on the disease are being compared, both similarities and differences. In case there are differences, the model is adjusted by changing the equations to minimize the differences as much as possible.

Claim 1, step (e) recites "checking the drug for cumulative effects and providing this information to the computer model". It is unclear as to what cumulative effects are being "checked". Clarification is requested.

Cumulative effects are the effects of drug on both disease and organism after it was administered more than once, taking into account the previously administered amounts. Note that administering a certain amount of drug once, might have different effects (less or more) than administering the same total amount in several times.

Claim 1, step (g) recites "determining an optimal protocol for the most responsive patient populations and indications for phase II clinical trial". It is unclear what is intended by this step.

Does applicant intend that the claim read determining an optimal protocol for the most responsive patient populations and indicating a phase II clinical trial based upon some criteria? Clarification is requested.

In this application the term 'indication' should be understood according to its meaning in medicine. The following is the definition of 'indication' from Webster's 1913 dictionary:

5. (Med.) Any symptom or occurrence in a disease, which serves to direct to suitable remedies.

To further clarify the subject matter, the Applicants amend the claims to replace 'indication' by 'clinical indication.' For example, in case that the disease is cancer a clinical indication could be breast cancer, or lung cancer, which is another clinical indication. Step (g) results involve determining an optimal treatment protocol for different pairs of a clinical indication and a patient population, based on the outcomes of the simulations of step (f),

For example, the optimal (most promising) treatment protocol with Doxorubicin for breast cancer in Asian women is different from the optimal treatment protocol with Doxorubicin for same indication, breast cancer, in Caucasian women. Similarly, the optimal treatment protocol (regimen) for the lung cancer indication may be different for the subpopulations of smokers and non-smokers. Furthermore, the two optimal treatment protocols for different subpopulations with the breast cancer indication may be completely different from the optimal treatment protocols for the different subpopulations with lung cancer indication.

Claim 1, step (h) recites "performing phase II clinical trial where a number of small scale clinical trials are performed in parallel based upon the results of step g. It is unclear as to what results the claim refers? What results in step g are being used? Clarification is requested.

As explained above step (g) provides different optimal treatment protocols **predictions** for different pairs of a clinical indication and a patient population. For each prediction of an optimal treatment protocol, a phase II clinical trial is performed applying the optimal treatment protocol to patients belonging to the appropriate patient subpopulation having the appropriate clinical indication.

Claim 1, step (i) recites "analyzing interim results to choose the most promising regimens for continued clinical trials". It is unclear what is intended by "interim results". At what point are results analyzed to choose the most promising regimens? Further, what constitutes a "most promising regimen"? Clarification is requested.

Analyzing "interim results" means analyzing "the results of phase II clinical trials performed in step (h)".

After conducting phase II clinical trials of step (h) for the various different treatment protocols, the researcher has real life verification (apart from the predictions provide by the simulations of step (f) according to which these treatment protocols were chosen for the trials) of the overall effectiveness of the treatment protocols. Most promising regimens (=treatment protocols) are defined by the drug developer who conducts the clinical trial. He can account only for effectiveness of the treatment regimen i.e. best effect on the disease. For example, in cancer a significant reduction in tumor size is considered as an indicator of effectiveness. On the other hand drug developer may want to account for effectiveness as well as toxicity effects.

Claim 1, step (j) recites "performing phase III clinical research for chosen indications by chosen protocols". There is insufficient antecedent basis for "chosen indication" and "chosen protocols". Further, what indication and what protocols are intended? Clarification is requested.

Claim 1, step (k) recites "performing phase IV studies for post-marketing subpopulation analysis and long term product safety assessment". It is unclear what the relationship is between the phase IV studies and post marketing and product safety. Clarification is requested.

See the explanation below from wikipedia (http://en.wikipedia.org/wiki/Clinical_trial) regarding phase IV of clinical trials.

Phase IV trials involve the post-launch safety surveillance and ongoing technical support of a drug. Phase IV studies may be mandated by regulatory authorities or may be undertaken by the sponsoring company for competitive or other reasons. Post-launch safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and timescale than was possible during the initial clinical trials. Such adverse effects detected by Phase IV trials may result in the withdrawal or restriction of a drug - recent examples include cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).

Claim 2 recites "wherein step b, prior to each sub-step of the phase I trial". There is insufficient antecedent basis in the claim for "each sub-step", as no sub-step is recited in step (b). Clarification is requested.

Indeed the sub-step is not a sub-step of claim 1 step (b), but as clearly indicated in the claim a sub-step of Phase I clinical trial. As indicated in Claim 1 step (b): " performing a phase I clinical research in which a clinical trial on at least single dose is performed..". Usually it is

performed for many possible doses to decide the Maximal Tolerated Dose of the drug. Claim 2 relates to each such trial with a different dose as a sub-step of Phase I.

Claim 2 recites "the computer model is adjusted based upon the comparison". It is unclear as to what about the comparison is used to adjust the computer model. Clarification is requested.

As explained in issue 1 above, regarding the comparison, which requires model adjustment. The researcher compares the results of the real life studies to the predictions of the model. In case these prediction turn out to be not as accurate as required, the model should be changed/ adjusted so that it gives more accurate results. The models are adjusted by changing the equations to result different outcomes to the same calculations.

Claim 3 recites "the method of claim 1, wherein a first decision whether to continue with the trial is made, stopping the trial if an adverse decision is made". It is unclear to what "trial" this step pertains. Further, where does this step occur in the claimed method?

The term 'trial' in this step refers to clinical trial. The first decision is whether to continue the clinical trial and proceed to Phase II. This decision is taken prior to step (h) of claim 1 which involves the performing of Phase II.

Claim 4 recites "the method of claim 1, wherein results of step g are used to define indication and define sub-groups of patients". It is unclear as to what "indications" are intended.

See definition of 'indication' given in the answer to issue 5 above.

Claim 5 recites "effective treatment protocol". Is in unclear what defines the metes and bounds of "effective treatment". Clarification is requested.

Effective treatment protocol (regimen) is one that has a desired effect on the disease. The metes and bounds are not generally set. They are of course disease dependent, where, in cancer a

conventional measurement for the effectiveness of treatment is the decrease in tumor size and the period of recession. They are set by practitioners in the specific medical field.

Claim 7 recites "the small clinical trials are performed in parallel for a chosen indication by a chosen treatment protocol". It is unclear as to what "indication" the claim refers. Clarification is requested.

See definition of 'indication' given in the answer to issue 5 above.

Claim 9 recites "a second decision". This is unclear, as no first decision was determined. Clarification is requested.

First decision was mentioned in Claim 3 and as explained above referred to the decision whether to continue to the Phase II clinical trials. The second decision refers to the decision whether to continue to the Phase III clinical trial.

Claim 11 recites "efficacy profile". It is unclear what is intended by and "efficacy profile", as no such profile is defined in the specification. Clarification is requested.

The term 'efficacy profile' of a drug is widely used by pracititioners in the biopharmaceutical industry (google search results more than 18 million results) along with 'safety profile'. It relates to the features of the drug for which it shows to be effective, say the range of dosage, clinical indications etc., for which the drug is effective.

Claim 14 recites "the method of claim 1, when hitherto unknown effects are discovered, the computer model is adjusted to obtain predictions for new protocols, patient population, and indication". It is unclear as to when this step is performed within the steps of the claimed method. What predictions are obtained? What indications are indicated? Clarification is requested.

This step is performed in step (j)-phase III of the claimed method. The predictions are the predictions provided by simulating the adjusted/modified model. The indications are again as defined in the answer to Claim 1 step (g) above.

Claims Rejections Under 35 U.S.C.§ 112, first paragraph

Rejection of Claims 1-9, 11 and 13-17 under 35 U.S.C. § 112, first paragraph

The Applicants respectfully submit that the Examiner is incorrect in her contention that the present invention is enabled only for cancer. Many of the significant steps are described further above in relation to the rejection under section 112, first paragraph. A skilled artisan reading the Specification would have known that the present invention is of a general nature and the techniques are workable regardless of the specific disease under consideration.

Claim Rejections Under 35 U.S.C. § 102

Rejection of claims 15-17 based on Iliadis et al.

In rejecting the claims based in Iliadis, the Examiner contends that Iliadis discloses that the protocols are used clinically. However, claims 15-17 are related to **interactive clinical trials.** A general teaching that protocols are used clinically as in Iliadis cannot be construed to be a specific disclosure related to interactive clinical trials.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131 *citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed.

Cir. 1987). The present invention, as recited in claim 1 (as amended), is not anticipated by Iliadis at least because of the above noted differences.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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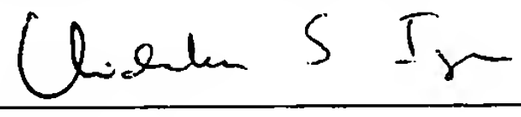
Respectfully submitted,



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